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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,725	11/16/2000	Ying Luo	RIGL-008CIP	6653

24353 7590 08/08/2003

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UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	20

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/715,725	Luo et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 23, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26, 27, and 29-32* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26, 27, and 29-32* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *6,7*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed May 23, 2003) in response to the Office Action of February 25, 2003 (Paper No. 16) is acknowledged and has been entered. Previously pending claim 28 has been canceled, claims 26-27, 29-30 have been amended, new claims 31-32 have been added. Claims 26-27, 29-32 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. It is noted that the Office Action Summary sheet showed that Paper No. 16 was made final. However, it is clear from the action mailed, that the indication of a final rejection on the Office Action Summary sheet was an inadvertent typographical error because the Action itself never mentioned any finality and was not made final. Examiner apologizes for any inconvenience.

4. The following rejections are maintained:

Claim Rejections - 35 USC § 112

5. Claim 27 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 16, Section 4, pages 3-5.

Applicant states that the rejection of claim 27 under 35 USC 112 first paragraph has been adequately addressed in view of the remarks set forth above. However, the remarks set forth above are drawn to a repetition of Examiner's grounds of rejection, a change in the dependency of claim 27. It is not clear how these remarks address the rejection of record. Further, although Applicant has amended claim 27 to recite that the polypeptide comprising an amino acid sequence having at least 90% identity to the sequence set forth in SEQ ID NO:8 wherein said recombinant ING2 protein binds to an inhibitor of apoptosis protein (IAP), this amendment is not sufficient to overcome

the rejection of record because neither the specification nor the art of record teaches **which** IAP the polypeptide of SEQ ID NO:8 binds to, the claim does not require that the 90% polypeptide bind to the same IAP that SEQ ID NO:8 putatively binds to. It is noted that although the specification recited IAPs cIAP1 and cIAP2, numerous IAP proteins are known. For example, Salvesen et al (Nature Reviews Molecular Cell Biology, 2002, 3:401-410) specifically teaches that IAPs were first described in 1993 and that since that time, this discovery has led to the identification of cellular orthologues in species as diverse as yeast, nematode, flies and humans (p. 401, col1). Although the reference does not disclose how many different species express IAPs or how many IAPs are expressed in each species, since neither the specification nor the claims are limited to human IAPs, the number of IAPs that meet the limitation of these claims could well be in the hundreds. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus that bind to SEQ ID NO:8, since the specification does not enlighten the artisan as to which of the numerous known and not yet discover IAPs that SEQ ID NO:8 binds to, does not identify a structure within SEQ ID NO:8 that is associated with the binding function, the disclosure of the single specific amino acid sequence is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. The rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

6. Claims 26-27, 29-32 are rejected under are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific asserted utility, a well established utility or a substantial utility.

The disclosed utility for the ING2 protein encoded by SEQ ID NO:7, SEQ ID NO:8, a variant thereof, a recombinant ING2 protein comprising an amino acid sequence having at least 90% sequence identity to the sequence set forth in SEQ ID NO:8, wherein the claimed protein binds an IAP includes screening for bioactive agents capable of interfering with the binding of a cell cycle protein and the IAPs, screening for bioactive agents that modulate the activity of a cell cycle protein (p. 3), its use in an assay to screen for a bioactive agent capable of modulating apoptosis, its use in an assay to screen for a bioactive agent capable of modulating the cell cycle (p. 4), its use in a two hybrid system to detect protein-protein interactions (p. 42), inducing or preventing cell proliferation in cells (43), its use in the diagnosis, treatment, prevention of cell cycle associated disorders, preferably cancer (p. 44). The asserted utility of the claimed protein appears to be based on the assertion that SEQ ID NO:7 which encodes ING2 isoform SEQ ID NO:8 encodes a cell cycle protein and that a preferred embodiment is one in which the cell cycle protein binds to at least one inhibitor of apoptosis protein (p. 2, lines 10-24) and that therefore, variants of SEQ ID NO:8, proteins with 90% identity to the SEQ ID NO:8 are cell cycle proteins. It is noted that there is no teaching or evidence in the specification or in the art of record that SEQ ID NO:8 proteins are in any way associated with the cell cycle or with apoptosis. There is no disclosure of why Applicants think that SEQ ID NO:8 binds to an IAP. Thus, the invention lacks substantial utility because additional experimentation

must be done to determine whether or not SEQ ID NO:8 is involved in any way with apoptosis or if it binds to an IAP. Further, even if the protein encoded by SEQ ID NO:7 is a cell cycle protein and utility of the encoded protein were to be associated with its designation as a cell cycle protein, this designation applies to many unrelated polypeptide structures sequences as well as different function and therefore the SEQ ID NO:8 polypeptide lacks specific utility. Further, the assignment of SEQ ID NO:7 which encodes SEQ ID NO:8 as encoding a cell cycle protein appears to be based on the homology of the ING2 isoform to the polypeptide encoded by the ING1 gene, which, according to the specification **may be** (emphasis added) linked to negative regulation of cell proliferation, the control of cellular aging, anchorage dependence and apoptosis because properties of ING1 **point to** (emphasis added) several regulatory functions of the cell cycle. However, other than pointing to a general hypothesis, the specification does not teach any particular function of the ING1 gene product. Thus, the ING2 isoform, even if it is an ING1-like proteins, does not have a well established utility because at the time the invention was made, no well-established utility appears have been known for the ING1 gene product. Further, although a review of the literature has revealed homology of the polypeptide encoded by SEQ ID NO. 7 to ING1, that homology is very limited. SEQ ID NO:8 shares 36.5% local similarity with 33.6% of the ING1 polypeptide, or 12.3%. Thus the designation of SEQ ID NO:8 as a cell cycle protein is based on overall homology of SEQ ID NO:8 to ING1 of 12..3%. Further, although the identity is 12.3%, the lack of identity of SEQ ID NO:8 to ING1 is 87.7%. Given that the specification teaches that cell cycle proteins can be identified by substantial amino acid sequence identity or similarity (greater than 75% to about

98% identity) to the sequences ID NO:8, as shown in Figure 8 (p. 7, lines 31-35). It would appear that, by the teaching of the specification, the ING1 gene product is not a cell cycle protein. If the ING1 gene product is not a cell cycle protein and the designation of the ING2 isoform as a cell cycle protein is based on homology to the ING1 gene product, then SEQ ID NO:8 could not have a well established utility, even if it were to be determined that the ING1 gene product is a cell cycle protein. In such a case, additional research would be required in order to determine if the SEQ ID NO:8 is cell cycle proteins and the invention does not have substantial utility. In addition, Bowie et al, (Science, 1990, 257:1306-1310), teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast

growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al, of record, who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with an 87.7% dissimilarity with the ING1 gene product, even if the ING1 gene product were a cell cycle protein, the function of SEQ ID NO: 8 could not be predicted, based only on sequence similarity with the ING1 gene product, nor would it be expected to be the same as that of the ING1 gene product. In addition, Bork (Genome Research, 2000,10:398-400), clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous.

Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 87.7% dissimilarity, to the ING1 gene product, the function of the Seq ID NO: 8 polypeptide could not be predicted, based on sequence similarity with ING1 gene product, nor would it be expected to be the same as that of ING1 gene product. Further research would be required to establish a function for the polypeptides, thus the invention does not have substantial utility.

In addition, the specification teaches that the encoded polypeptide is useful for assays to determine binding of proteins to the cell cycle protein and screening for agents that modulate activity of the cell cycle protein, generating. However, neither the specification nor any art of record teaches what SEQ ID NO:8 is, what it does,

does not teach a relationship to the cell cycle. Thus, for the reasons set forth above, additional experimentation is required to determine whether or not SEQ ID NO:8 is in any way involved with the cell cycle, thus the invention does not have substantial utility.

The specification further teaches that the SEQ ID NO:8 is useful in the study or treatment of conditions which are mediated by the cell cycle proteins, i.e. to diagnose, treat or prevent cell cycle associated disorders and these disorders include conditions involving both insufficient or excessive cell proliferation and preferably cancer (p. 44). In addition, the specification teaches general methods of diagnosing cell cycle related conditions including assaying for differences in amount or specific activity of a cell cycle protein (p. 44-45), assaying the levels of cell cycle protein genes (p. 45-48. However, neither the specification nor any art of record teaches what SEQ ID NO:8 is, what it does, does not teach a relationship to any specific disease or establish any involvement of SEQ ID NO:8 in the etiology of any specific disease or the involvement of any of the encoded polypeptides with apoptosis. It is clear that additional work must be done in order to determine if the encoded polypeptide is in any way associated with any disease state or with apoptosis, thus SEQ ID NO:8 does not have substantial utility.

Further, as drawn the encoded protein, SEQ ID NO:8, neither the specification nor the art of record teaches that SEQ ID NO:8 is actually expressed *in vivo.* Since the "cell cycle protein" appears to be novel, it appears that the novel protein was identified by the homology of a consensus sequence synthesized from ESTs when compared to public databases (see page 6). It is thus unknown whether SEQ ID NO:7

is actually found *in vivo*, it is unknown, if found *in vivo*, whether or not SEQ ID NO:8 is expressed *in vivo*. Thus, the invention does not have substantial utility because it must be ascertained whether or not SEQ ID NO:7 is actually found *in vivo* or whether SEQ ID NO:8 is expressed *in vivo,* in order to determine a utility for the claimed invention. In particular, as drawn to the expression of the protein, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on

mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict, even if SEQ ID NO:7 is found *in vivo*, if SEQ ID NO:8 could in fact be translated into a polypeptide expression product. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Finally, as drawn to claims 27 and 30-32 wherein said claimed proteins bind to an inhibitor of apoptosis protein. Although the specification states that a preferred limitation is that SEQ ID NO:8 binds to an IAP, neither the specification, nor the art of record teaches any association of SEQ ID NO:8 with an IAP, there is no teaching as to why it is suggested that a preferred limitation is that SEQ ID NO:8 binds to an IAP. Is this wishful thinking? There is no evidence in either the specification or in the art of record that suggest that this preferred limitation is in any way possible for SEQ ID NO:8 or the variants or 90% homologs claimed. There is no teaching or any suggestion of which of the family of IAP, the claimed invention would be expected to bind to. Thus, the invention does not have substantial utility, because additional work must be done to determine whether or not SEQ ID NO:8 binds to an IAP and if it does bind to an IAP, which one or ones it does bind to.

Since SEQ ID NO:8 does not have specific utility, well established utility or substantial utility, it is clear that none of the variant or 90% homologs of SEQ ID NO:8 have specific utility, well established utility or substantial utility. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the claimed assay. Because the claimed invention is not supported

by a specific utility, well established utility or substantial utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

8. Claims 26-27, 29-32 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a specific utility, a substantial utility, a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

9. If Applicant were able to overcome the 35 USC 101 and 35 USC 112, first paragraph rejections above, Claims 27 and 31-32 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a recombinant ING2 protein encoded by the contiguous polynucleotide sequence of nucleotides 120-845, SEQ ID NO:8, does not reasonably provide enablement for a recombinant ING2 protein which is a variant of SEQ ID NO:8 a recombinant ING2 protein comprising an amino acid sequence having at least about 90% sequence identity to the sequence set forth in SEQ ID NO:8 or an isolated protein thereof which has a sequence set forth in SEQ ID NO:8. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

It is noted that for examination purposes, the limitation "wherein said isolated protein has **a** sequence set forth in SEQ ID NO:8" is interpreted to mean that the claim encompasses a sequence set forth in SEQ ID NO:8, that is a sequence of 2, 3, 4 amino acids of SEQ ID NO:8.

The claims are drawn to variants of SEQ ID NO:8 which bind to an inhibitor of apoptosis protein as well as proteins that have a sequence set forth in SEQ ID NO:8 which binds to an inhibitor of apopotosis protein. The specification teaches that it is desirable to identify cell cycle components and modulators and there is a deficit in the field of such compounds, it would be advantageous to provide novel compositions which are involved in the cell cycle (p. 2, lines 5-9). In a preferred embodiment a protein is a cell cycle protein as defined in the specification if the overall sequence identity of the amino acid sequence is preferably greater than 75% to about 98% (p. 7, lines 31-35). Variants fall into one or more of three classes, substitutional, insertional or deletional variants. The variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, although variants can also be selected which have modified characteristics (p. 13, lines 11-24). One cannot extrapolate the teaching of the specification to the scope of the claims because protein chemistry is probably one of the most unpredictable areas of biotechnology. Although the specification teaches that variants fall into one or more of three classes, substitutional, insertional or deletional variants, the specification fails to teach what deletions, substitutions and insertions can be made to SEQ ID NO:8 and have it still function as

claimed. In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Further, neither the specification nor

the art of record informs the artisan as to which of the plethora of known and unknown IAPs SEQ ID NO:8 binds to. No consensus binding sequence is taught. Even if SEQ ID NO:8 binds to and IAP it could not be determined from the information in the specification, even if the variant bound to an IAP, whether that IAP was the same as that bound by SEQ ID NO:8. Clearly, with a minimum of 10% dissimilarity, to SEQ ID NO:8, the function of the polypeptide comprising 90% identity to SEQ ID NO:8 could not be predicted, based on sequence similarity with SEQ ID NO:8, nor would it be expected to be the same as that of SEQ ID NO:8 in the absence of guidance in the specification as to which residues were critical for function. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention

10. If Applicant were able to overcome the rejections under 35 USC 101 and USC 112, first paragraph above, Claims 27 and 30-32 are rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a recombinant ING2 protein, SEQ ID NO:8 which binds to an inhibitor of apoptosis protein (IAP). The specification repeatedly states that the ING2 protein, SEQ ID NO:8, binds to an IAP. The specification further teaches that variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, although variants can also be selected which have modified characteristics (p. 13, lines 11-24). One cannot extrapolate the teaching of the specification to the enablement of the claims because in not a single instance is there a

nexus made between any of the variants and binding to any IAP. No consensus sequence for IAP binding is taught or required in the claims and the specification does not teach which of the myriad IAPs SEQ ID NO:8 or the claimed variants binds to. In particular, Salvesen et al (Nature Reviews Molecular Cell Biology, 2002, 3:401-410) specifically teaches that IAPs were first described in 1993 and that since that time, this discovery has led to the identificatin of cellular orthologues in species as diverse as yeast, nematode, flies and humans (p. 401, col1). Although the reference does not disclose how many different species express IAPs or how many IAPs are expressed in each species, since neither the specification nor the claims are limited to human IAPs, the number of IAPs that meet the limitation of these claims could well be in the hundreds.

Finally, it is unclear why the specification suggests that SEQ ID NO:8 binds to an IAP since no information drawn to the assignment of SEQ ID NO:8 to the family of IAP binding proteins has been presented. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that any of SEQ ID NO:8 or the variants claimed bind to an IAP with a reasonable expectation of success. In the absence of adequate guidance in the specification, for the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

11. Claims 27 and 30-32 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a variant or protein comprising an amino acid sequence having at least

90% identity to SEQ ID NO:8 "binds to an inhibitor of apoptosis protein (IAP) has no clear support in the specification and the claims as originally filed. A review of the specification revealed support for the cell cycle protein provided herein binds to at least one inhibitor of apoptosis protein (p. 2, lines 15-19). Although the specification repeatedly discloses general information about variants, in not a single instance is there a nexus made between any of the variants and binding to IAP. In particular, the specification teaches that variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, although variants can also be selected which have modified characteristics (p. 13, lines 11-24). Nowhere is it suggested that the binding of the variant to IAP is the "qualitative biological active". The subject matter claimed in claims 27 and 30-32 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

12 The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 31 and 32 are rejected under 35 USC 102(b) as being anticipated by Tam et al, (Cancer Research, 1998, 58(23)5315-5320) as evidenced by Van de Craen et al (Y13086), Genbank Sequence Database (Acession Y13086), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available 1997 and Van de Craen et al (Y13088), Genbank Sequence

Database (Acession Y13088), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available 1997.

The claims are drawn to a variant of SEQ ID NO:8 wherein said isolated protein binds to an inhibitor of apoptosis protein (IAP) wherein said isolated protein has a sequence set forth in SEQ ID NO:8.

It is assumed for examination purposes that a cell cycle protein is a protein as defined in the specification, that is that a cell cycle protein may be identified by its association with a protein known to be involved in the cell cycle (p. 6, lines 15-19). A cell cycle protein is defined as having one or more of the following characteristics including binding to at least one IAP. Further, it is assumed that since SEQ ID NO:8 is defined as a cell cycle protein, that any cell cycle protein that binds to an IAP that has a sequence set forth in SEQ ID NO:8 (that is two or more contiguous amino acids) is a variant of SEQ ID NO:8 and meets the limitations of the claims.

Van de Crean, 1997, teaches the amino acid sequence of caspase 3 which has a sequence set forth in SEQ ID NO:8 (see EE and KK, highlighted).

Van de Crean, 1997, teaches the amino acid sequence of caspase 3 which has a sequence set forth in SEQ ID NO:8 (see EE and AA, highlighted).

Tam et al teach caspase-3 and -7 which are proteins involved in the cell cycle and each of which comprises a sequence set forth in SEQ ID NO:8 which are associated with a protein involved in the cell cycle, survivin. Both caspase-3 and caspase-7 bind to survivin, all of the limitations of the claims are met.

14. All other objections and rejections set forth in Paper No. 15 are withdrawn.

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
August 5, 2003